Focus on the locus network with 7T MRI: link to memory (dys)function

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON47689

Source
ToetsingOnline

Brief title
Locus coeruleus and memory (LoCoM)

Condition

- Other condition

Synonym
Alzheimer's disease; dementia

Health condition

prodromale fase van de ziekte van Alzheimer / preklinische fase

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Vernieuwingsimpuls;VENI

Intervention

Keyword: Dementia, Locus coeruleus, Memory, Noradrenalin

Outcome measures

Primary outcome

The main outcome measures are performance on the MRI-task (mean reaction time and accuracy), the Blood Oxygen Level Dependent (BOLD) response, reflecting brain activity during the functional task., episodic memory performance and noradrenalin levels.

We will investigate i) how the locus coeruleus interacts with other brains areas during memory performance and how this is different in Alzheimer's disease patients compared to healthy older individuals; ii) how noradrenalin levels change during memory performance and how they interact with brain functioning; and iii) which parts of the memory-related brain networks are influenced by applying transcutaneous vagus nerve stimulation once, and whether this might be different for Alzheimer's disease patients whose brain functioning is compromised.

Secondary outcome

Our secondary objectives pertain to the anatomical properties of the locus coeruleus.

The outcome variables are: grey matter volume and shape properties and their correlation to neuropsychological performance.

The associated research questions are

1. Is there a difference in grey matter volume and shape properties of the

locus coeruleus across the two groups?

2. Do morphological group differences relate to neuropsychological performance?

Study description

Background summary

The cause of Alzheimer*s disease, the most common form of dementia, remains unknown. Neuropathological studies suggest that a small area in the brainstem, the locus coeruleus, might be the site of the onset of the disease. This area is the sole soure of noradrenalin to the brain, a neurotransmitter involved in arousal, but also cognitive functions. Animal and pharmacological studies have hinted towards an important role of this area in memory functioning. However, these studies were hampered by the limited spatial resolution, making it hard to clearly localize the locus coeruleus in the brain. New developments in brain imaging allow now to visualize the brain with stunning precision. Furthermore, a non-invasive new stimulation method, transcutaneous vagus nerve stimulation, is believed to excite the locus coerulues and thereby influencing neuronal networks and memory functioning.

Study objective

There are three aims in this project:
1. To investigate how the functional interaction between the locus coeruleus and other brain areas, in particular the medial temporal lobe areas, during memory processes (encoding, consolidation and retrieval) change with development of Alzheimer's disease.
2. To investigate associations between noradrenaline, memory performance and brain functioning. We aim to investigate how acute noradrenalin levels change during the different memory processes and whether or not this is beneficial for performance. Furthermore, we will investigate whether this interaction between noradrenalin, memory performance and brain functioning is different healthy older individuals or patients with prodromal Alzheimer's disease.
3. To investigate the underlying neural network changes during transcutaneous vagus nerve stimulation. We will focus on differences in functional connectivity between the locus coeruleus and the medial temporal lobe areas in healthy older individuals and prodromal Alzheimer's disease patients. An experimental condition will be compared with a sham condition in a

pseudo-randomized cross-over design.

Study design

This is an observational MRI study with a pseudo-randomized cross-over design for the stimulation part.

Study burden and risks

We do not expect that the participants are at any risk during this study and we do not expect them to benefit from this study directly. Participants will be screened for claustrophobia or related anxiety problems. In case of doubt, the dummy scanner will be a check to investigate possible fears. The participants will be informed about unexpected medical findings. In case the participant does not wish to be informed, he is not allowed to participate in this study.
A static magnetic field of up to 14T or more does not harm biological tissue, but the radiofrequency and MR gradient applied can influence the human body via heating (specific absorption rate (SAR)). Just as with 1.5T and 3T MRI scanners the limits of the radiofrequency (RF) and magnetic resonance (MR) gradient are encoded in the 7T scanner. Therefore certified users will always stay below these limits making 7T scanning harmless. Furthermore, just as with 1.5T and 3T MRI scanners, metallic objects cannot be inserted into the scanner area of the 7T MRI scanner. Therefore, subjects with metallic prostheses, pacemakers, metal clips on blood vessels, metal parts in the eye, an intrauterine device, metal braces and other metal objects will be excluded from the study. Prior to scanning all subjects will fill out a form to screen for these metallic objects. Although 7T MRI is harmless if contra-indications are taken heed of and if operated by certified users, a small amount of people (5%) may experience vertigo or nausea while entering the scanner. However, these symptoms will be minimised by slowing the subject*s entry and exit time into the magnetic field.
As for the transcutaneous vagus nerve stimulation: The TENStem device is CE certified and registered for this purpose and several studies have applied it successfully in healthy subjects (including older participants), patients and in the MRI environment. For the administration, we will adhere to the reported parameters and location (left ear). Participants who do not tolerate these parameters will be excluded from the study.
Even though, this device has been used previously in an MRI context, we will not start this study before the safety committee of Scannexus has formally approved its compatibility. Scannexus provides continuous support by trained lab workers, who are also able to deliver medical support if necessary. Transcutaneous vagus nerve stimulation has no known complications and no long-lasting or serious adverse events. We will however monitor heart rate, blood pressure, and enquire potential sensations after stimulation. For safety reasons (both for the MRI and stimulation), we will exclude participants with cardiac pathology or pace makers. The risk for the participant involves

temporary light dizziness (15%), concentration problems, fatigue or a tingling sensation at the ear.
We are convinced that the risks are acceptable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For the patients:
- diagnosis of prodromal Alzheimer's disease based on the latest research criteria
- Clinical Dementia Rating score of 0.5
- Mini-Mental State Examination (MMSE) score of 23 and being mentally competent
- Age: between 60 and 85 years old
- 50% female
- Right-handedness

- Average level of education (CBS level 3-4-5-6)
- Informed consent before participation in the study;For the healthy older individuals:
- Average neuropsychological test results
- No substantial memory complaints (according to the participant)
- Age: between 60 and 85 years old
- 50% female
- Right-handedness
- Average level of education (CBS level 3-4-5-6)
- Informed consent before participation in the study

Exclusion criteria

- Strong reduced vision
- Psychoactive medication use
- Abuse of alcohol and drugs
- Cognitive impairment due to alcohol/drug abuse or abuse of other substances
- Past or present psychiatric or neurological disorders (major depression, schizophrenia, bipolar disorder, psychotic disorder (or treatment for it), epilepsy, stroke, Parkinson*s disease, multiple sclerosis, brain surgery, brain trauma, electroshock therapy, kidney dialysis, Menière*s disease, brain infections)
- Major vascular disorders (e.g. stroke)
- Heart diseases or pacemakers
- Contraindications for scanning (e.g. brain surgery, cardiac pacemaker, metal implants, claustrophobia, body tattoos)

Study design

Design

Study type:	Observational non invasive
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	18-01-2017
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	22-04-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-06-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT:nognietvrijgegeven(nagoedkeuringMETC)
CCMO	NL51297.068.14